MANAGEMENT OF FEBRILE NEUTROPENIA

DEFINITION

FEVER
> 38 deg C on two consecutive occasions > 1 hour apart OR
> 38.5 deg C on one occasion

AND

NEUTROPENIA
a neutrophil count of <0.5 x 10^9/L OR
recent intensive chemotherapy where neutropenia is expected

EVALUATION OF PATIENT

- Take History and examine patient
- Full blood count, urea and electrolytes (with reference to when last chemotherapy given)
- Culture blood from all lumens (prior to administration of antibiotics)
- Peripheral culture may be indicated
- Culture other sites as clinically indicated
- Chest X-ray/urine as clinically indicated
- Sputum/NPA as clinically indicated
- Check MRO (multi-resistant organisms) status and/or for clinical alerts

INITIAL TREATMENT:

Antibiotic therapy to be commenced within 1 hour of presentation (or fever spike if inpatient)

<table>
<thead>
<tr>
<th></th>
<th>Piperacillin/ Tazobactam* 100mg/kg q6h (combined product)</th>
<th>Vancomycin 15mg/kg q6h</th>
<th>Amikacin 20mg/kg q24h</th>
<th>Meropenem 40mg/kg q8h</th>
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</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td></td>
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<td></td>
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<tr>
<td>+ High dose cytarabine AML therapy</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>+ History of ESBL**</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Shocked patients***</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Suspected meningitis</td>
<td></td>
<td>✓</td>
<td>✓</td>
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</table>

* For patients with minor penicillin allergy (rash or similar); substitute cefepime 50mg/kg q8h (max 2g/dose) (or if unavailable, ceftazidime 50mg/kg q8hr (max 2g/dose) plus vancomycin 15mg/kg q6h)
** For patients with previous life threatening penicillin reaction; substitute ciprofloxacin 10mg/kg q8h plus vancomycin 20mg/kg q8h
*** For ESBL with known resistance to amikacin, use meropenem alone 40mg/kg q8h (max 2g/dose)
**** If on-going cardiovascular instability (hypotension OR tachycardia OR signs of inadequate organ perfusion) following 40ml/kg of intravenous fluid resuscitation contact Intensive Care.
The empiric protocol for all febrile neutropenic patients is monotherapy with **piperacillin/tazobactam (Tazocin)** 100mg/kg q6h (combined product), max 4.5g per dose, and subject to the following exceptions.

- For patients who have been treated with high dose cytarabine (HD ARA C), are on AML therapy or for BMT inpatients, add **vancomycin** 15mg/kg q6h due to high risk of streptococcus mitis infection
- For patients who are shocked (multiple fluid boluses or PICU), add **amikacin** 20mg/kg q24h (max 1.5g/dose) and **vancomycin** 15mg/kg q6h (max 1g/dose)
- For patients known to have any ESBL colonisation add **amikacin** 20mg/kg q24h (unless known resistance to **amikacin** in which case substitute **meropenem** 40mg/kg q8h (max 2g/dose)
- For patients who had exposure to Cisplatin, avoid **amikacin** due to risk of renal impairment
- For patients with suspected meningitis, use **meropenem** 40mg/kg/q8h and **vancomycin** 20mg/kg q8h
- For patients with low risk febrile neutropenia after initial therapy who are suitable for outpatient treatment; **ceftriaxone** 80mg/kg q24h (max 2g) as a **single agent** may be considered

Note: when Vancomycin is prescribed it will most often be in combination with q6h Tazocin, our departmental practice will be for Vancomycin 15mg/kg q6h (max 1g/dose or 4g/day) and only in exceptional situations, such as suspected meningitis, it could be as Vancomycin 20mg/kg q8h (max 4g/day) in combination with meropenem 40mg/kg q8h.

### RISK GROUPS

**Please note:**
- If recent FBC not available, estimate which risk group the patient falls into based on previous chemotherapy, and start antibiotics per above
- Febrile patients with neutrophil count 0.5 – 1.0 x 10⁹/L should be evaluated for need for possible empiric antibiotics

<table>
<thead>
<tr>
<th>Absolute neutrophil count</th>
<th>LOW RISK</th>
<th>HIGH RISK</th>
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</thead>
<tbody>
<tr>
<td>Duration of neutropenia</td>
<td>0.1 – 0.5 x 10⁹/L</td>
<td>&lt;0.1 x 10⁹/L</td>
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<tr>
<td>Co morbidity</td>
<td>None</td>
<td>Toxic/Shocked</td>
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<tr>
<td></td>
<td></td>
<td>BMT Inpatient</td>
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<tr>
<td></td>
<td></td>
<td>AML patients</td>
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<tr>
<td>≥ 7-10 DAYS</td>
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**Evaluate at 48 hours:**
- All culture results should be reviewed and antibiotics adjusted according to isolates and antibiotic sensitivities
- If **afebrile** with negative cultures and still neutropenic, consider discharge home on **Ceftriaxone IV 80mg/kg (max 2g)** once daily. If high risk consider additional once daily **Amikacin 20mg/kg** until neutrophil counts start to increase or until neutrophil count > 0.5 x 10⁹/L
- Daily **ceftriaxone** is not recommended for inpatient use
- If cultures are negative for gram-positive organisms stop **Vancomycin** after 48 hours
- Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours, who have been febrile for at least 24 hours and who have evidence of marrow recovery.

**Note on microbiology regarding change in febrile neutropenic regimens:**
Pathogens that are not covered by **piperacillin/tazobactam** include 1) enterococcus, 2) coagulase negative staphylococcus, 3) Stenotrophomonas (This is, however, an environmental pathogen that is uncommonly seen, usually of a lower virulence, and can be treated with **Cotrimoxazole** or **Timentin** once culture result is available).
**Escalation of therapy:**

If patient is clinically well or improving, but persistently febrile at 24-72 hours, do not modify empiric antibacterial regime based solely on persistent fever. If there is clinical deterioration, change to meropenem and add vancomycin.

**Febrile at 48 hours:**
- If negative cultures, reassess and reculture, and if clinically appropriate, add vancomycin 15mg/kg q6h and adjust according to Vancomycin levels

**Febrile at 4-5 days:**
- Reassess and consider more invasive investigative procedures and imaging
- Consider switching to meropenem 40mg/kg q8h*
- In high risk children with persistent fever beyond 96 hours perform evaluation for invasive fungal disease (IFD), e.g. CT scan lung, brain and sinuses plus abdomen (if LFTs deranged) and other clinically suspected areas of infection
- Add Liposomal Amphotericin (AmBisome ®) IV 3mg/kg once daily*
  - Ambisome can be commenced before 4-5 days (at the discretion of the Paediatric Oncology consultant in conjunction with a Paediatric Infectious Disease Specialist) regardless of fever status for children who are neutropenic on steroids and with a prior history of prolonged antibiotics or otherwise considered high risk for IFD.
  - Close monitoring of electrolytes and renal function is essential every 24 to 48 hours
  - If renal impairment or previous adverse reaction to AmBisome consider Caspofungin and consult Paediatric Infectious Disease (ID) team.

**The use of other nephrotoxic antibiotics and sepsis means patients are at risk of renal impairment.**

*All patients with persistent fever on meropenem and/or empiric liposomal amphotericin should be discussed with Paediatric ID team*

Remember possibility of viral infection HSV, VZV, CMV, EBV, Adenovirus etc. Consider acyclovir IV 500mg/m2/dose q8h for children under 12 years, and 10mg/kg q8hr for children over 12 years.

### INDICATIONS FOR LINE REMOVAL

- Bacillus species infections
- Staphylococcus aureus infection (unwell or with persistent bacteraemia)
- Recurrent infection with the same organism in the same line
- Shock and sepsis in a neutropenic patient
- Tunnel infections
- Exit site infection with aspergillus or mycobacterium
- Fungal line infections
- Blood cultures still positive after 48-72 hours of IV antibiotics or failure to improve clinically
- Valvular vegetation/endocarditis
- Fever + hypotension after line flush
NURSING:

ADMINISTRATION GUIDELINES

- Starship nurses - please refer to Starship Guardrails Administration Guidelines
- Outreach nurses – please refer to your local hospital guidelines

MONITORING LEVELS

Amikacin:
- Trough levels required, take level prior to second dose and every 3 to 5 days if normal renal function. Aim for trough less than 1mg/L.
  - If impairment of renal function or other nephrotoxic agents being administered take levels more frequently
  - If trough levels high may need to space out dosage interval eg 24-36 hours
- Peaks not required for once daily dosing.

Vancomycin:
- Take trough level immediately prior to fourth dose and every 3 to 5 days if normal renal function and vancomycin levels within range
- Aim for trough: 10mg-15mg/L, up to 20mg/L in certain cases
- Peaks not required

Associated Documents:
- Starship Children’s Health Neutropenia Nursing Care
  [http://adhbintranet/ADHB%5FPolicies%5Fand%5FProcedures/ClinicalStarshipChildren’s/NeutropeniaNursingCare.htm](http://adhbintranet/ADHB%5FPolicies%5Fand%5FProcedures/ClinicalStarshipChildren’s/NeutropeniaNursingCare.htm)

Reference:
1. New Zealand Formulary for Children (NZFC) 2014
2. Febrile Neutropenia Guideline, The Royal Children's Hospital Melbourne 2014